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Proline-catalysed asymmetric aldol reaction in the room temperature ionic liquid [bmim]PF_6†

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Proline-catalysed asymmetric direct aldol reaction of different aromatic aldehydes with acetone and several other ketones in the room temperature ionic liquid 1-*n*-butyl-3-methylimidazolium hexafluorophosphate achieved good yields of aldolisation products with reasonable enantioselectivities, even when just 1–5% of proline was used as the catalyst; immobilisation of the catalyst in an ionic liquid phase offers simple product isolation and reuse of the catalytical system in subsequent reactions.

The aldol reaction is one of the basic organic transformations for the formation of new C–C bonds.[1] The synthetic value of the aldol reactions has been proven by their application in the total synthesis of natural products.[2]

There is a broad range of effective approaches leading to stereoselective aldol reactions.[3] The most promising of them, especially from an industrial point of view, deals with usage of the small organic molecules as enzyme mimics.[4]

In recent years, the proline-catalysed asymmetric direct aldol reaction in intermolecular fashion was investigated.[5] A strong solvent influence on the resulting enantiopurity of products was observed and anhydrous DMSO has been found to be the most suitable solvent.[5c] Indeed, the aldol-product of benzaldehyde with acetone, which was used as co-solvent, was obtained in 62% yield and 60% ee (*R*) in the presence of (*S*)-proline (30 mol%).[5c,d]

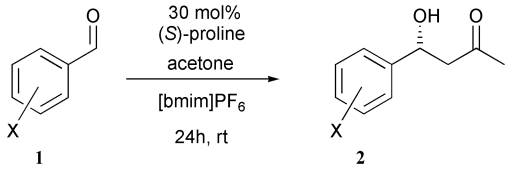
Two routes to catalyst recovery have been studied.[5d] The first method was based on the fact that proline is not soluble in chloroform. The reaction was performed in a heterogeneous manner and the catalyst was recovered by simple filtration. However, the product was obtained with lower enantioselectivity (in the case of *p*-nitrobenzaldehyde 61 *vs.* 76% ee). The second method was immobilisation of the catalyst on a silica surface and the resulting heterogeneous catalyst was applied to run reactions in DMSO–acetone (4:1) mixture. However, a significant reduction of enantioselectivity was also observed.

The advantages of proline based aldolisation are that the methodology is metal free and that both enantiomers of the catalyst are cheap and easily available. A possible limitation factor might be the utilisation of DMSO as the reaction solvent.

Room temperature ionic liquids have been applied as alternative solvents in many catalytical organic transformations.[6] The RTIL were also used recently for aldol reaction of propanal with 2-methylpentanal under NaOH catalysis.[7] Therefore, it was interesting to investigate the proline-catalysed direct asymmetric aldol reaction in ionic liquid and to compare the results with published data for more common organic solvents. The next important aspect was examination of the catalyst recovery and the possibility for catalyst reuse in subsequent reactions.

At first, several substituted benzaldehyde derivatives (**1**) were investigated and aldol reaction products (**2**) (Scheme 1) have been isolated after simple extraction of the reaction mixture.† The ionic liquid phase was dried *in vacuo* at 40 °C for 2 h and was used directly for subsequent reaction. The achieved results are summarised in Table 1.

The benzaldehyde (entry 1) aldol reaction product with acetone was obtained in 55% yield and 76% ee (*R*) in our case compared to 62% yield and 60% ee (*R*) from the literature.[5c] The regenerated catalyst gave product in 42% yield and 72% ee (entry 2). The next known case was *p*-nitrobenzaldehyde (entry 10), but we received much lower yield and enantioselectivity compared to results obtained in DMSO[5c,d] (21% yield, 48% ee *vs.* 68% yield, 76% ee). Nevertheless, by modification of the experimental procedure we were able to improve yield and enantioselectivity (68%, 65%ee, entry 12). The low yield of the product under the standard conditions could be caused by reaction of 4-nitrobenzaldehyde with the ionic liquid, as was suggested by one of the referees, and described in ref. 8. An experiment was therefore performed in which acetone was missing from the reaction medium. No reaction was observed, practically all 4-nitrobenzaldehyde was recovered and there were no aromatic chemical shifts in the ionic liquid used in this



1 **2**

Scheme 1

Table 1 Proline-catalysed aldol reaction in [bmim]PF_6 ionic liquid according to Scheme 1

Entry	X	Yield (%)[a]	ee (%)[b]
1	(H)	55	76
2	(2. run)	43	71
3	4-CF_3	91	73
4	(2. run)	75	67
5	(3. run)	74	63
6	4-F	90	68
7	(2. run)	87	61
8	4-OMe	69	50
9	(2. run)	52	48
10	4-NO_2	21	48
11	(2. run)	20	47
12[c]	4-NO_2	68	65
13	4-CN	74	70
14	(2. run)	71	46
15	2-Br	61	63
16	(2. run)	54	62
17	2-OMe	69	68
18	(2. run)	60	62
19	2-NO_2	93	82
20	(2. run)	86	54
21	3-NO_2	94	70

[a] Isolated yields after chromatography. [b] Determined by ^{1}H-NMR with chiral shift reagent Eu(hfc)$_3$ and/or by HPLC analysis (AD-H or AS Chiralpak® column). [c] Modified procedure: aldehyde was added after 30 min stirring of proline in acetone-ionic liquid mixture.

† Electronic supplementary information (ESI) available: experimental details and ^{1}H-NMR spectra of the prepared compounds. See http://www.rsc.org/suppdata/cc/b2/b206911c/

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reaction. A variety of 2- and 4-substituted benzaldehydes (**1**) have been employed and aldol products **2** were obtained in good yields (61–94%) and reasonable enantioselectivities (61–93% ee).

The recovered catalyst was reused and only a slight decrease of the chemical yields as well as enantioselectivities was observed, except for *p*-cyano (from 70 to 46% ee) and *o*-nitro (from 82% to 54% ee), where a significant drop of enantioselectivity was observed (entries 14 and 20). We do not have any reasonable explanation for this drop in selectivity. The reaction of 1-naphthalene-carbaldehyde with acetone gave, under the same conditions, aldolisation product in 55% yield and 68% ee compared to the 54% yield and 77% ee described for DMSO.[5c,d]

We next examined the influence of catalyst amount in the case of *p*-trifluoromethylbenzaldehyde (Table 2). No reaction took place in the absence of proline (entry 1). The same result was obtained with 10 mol% of proline compared to the reaction catalysed by 30 mol% of proline (entry 2). With 5 mol% of catalyst, the product yield remained at a comparable level, but with 1 mol% of catalyst the drop in reactivity was more significant (entries 3 and 4). In all cases the enantioselectivity was not affected (72–75% ee). Experiments with 1 mol% of (*S*)-proline were repeated several times and a serious drop in yield was observed after the third repetition (first reuse 75%, second reuse 75%, third reuse 30%). Nevertheless, the enantioselectivity of the reaction was preserved (75% ee) even after the eighth repetition. The addition of 0.5 mol% of catalyst to the reaction medium returned the yield to the original value (74%).

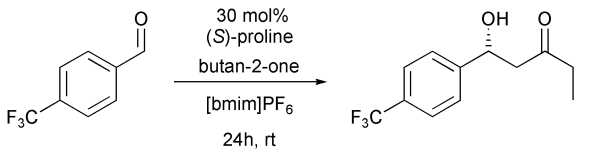
Proline-catalysed reaction of *p*-trifluoromethylbenzaldehyde with butan-2-one was also investigated (Scheme 2). The desired aldolisation product was isolated in 59% yield and 76% ee. The reused catalytical system gave product in 52% yield and 71% ee.

The reactions of *p*-trifluoromethylbenzaldehyde with cyclopentanone, cyclohexanone and cyclobutanone were also performed. Surprisingly, very different results were obtained (Table 3). The aldolisation of cyclopentanone resulted in ~1:1 mixture of *anti*- and *syn*-diastereomers, 32% ee for the *anti*-diastereomer and 86% ee for the *syn*-diastereomer (entry 1). However, cyclohexanone gave virtually pure *anti*-diastereomer (de >20:1) with high enantiopurity (93% ee) (entry 2). An attempt to reuse the catalytic system was made for the reaction with cyclohexanone, after the product was extracted from the ionic liquid, but the yield dropped to 67%. The diastereoselectivity of the reaction with cyclobutanone (entry 3) was reasonable, but enantioselectivity was, in this case, very low. The ee of the products were determined solely by ^{1}H-NMR spectra using a chiral shift reagent because the product decomposed upon transport for HPLC measurements in Koeln. No reaction was observed with cycloheptanone.

Table 2 Influence of catalyst amount on the reaction yield and enantioselectivity in the aldolisation of *p*-CF_3-benzaldehyde with acetone

Entry	(*S*)-proline (mol%)	Yield (%)[a]	ee (%)[b]
1	0	0	
2	10	92	72
3	5	89	74
4	1	74	75

[a] Isolated yields after chromatography. [b] Determined by HPLC analysis (AD-H Chiralpak® column).



Scheme 2 Proline-catalysed aldol reaction of *p*-CF_3-benzaldehyde with butan-2-one in [bmim]PF_6

Table 3 Proline-catalysed (30 mol%) aldolisation of *p*-CF_3-benzaldehyde with cyclopentanone (entry 1), cyclohexanone (entry 2) and cyclobutanone (entry 3)

Entry	Yield (%)[a]	de (%)[b] (*anti*:*syn*)	ee (%)
1	94	1:1	32 (*anti*) 86 (*syn*)
2	91	20:1	93 (*anti*) n.d. (*syn*)
3	53	6:1	10 (*anti*) 8 (*syn*)

[a] Isolated yields after chromatography. [b] According to NMR spectra of crude reaction mixtures.

Unfortunately, we were not able to detect aldol reaction products with acetophenone, pentan-3-one, 3,3-dimethylbutanal, dimedone and Meldrum's acid. Only condensation products and subsequent Michael addition by-products were detected after the reactions under standard conditions.

In conclusion, we have demonstrated that the room temperature ionic liquid [bmim]PF_6 is a suitable solvent for proline-catalysed asymmetric aldol reactions.

The catalyst immobilised in an ionic liquid phase is recyclable and in many cases the product yield and enantiopurity remained at a comparable level as in the case of the fresh catalyst. Further investigations in this laboratory involve the study of different proline-catalysed reactions in ionic liquids.

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